PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
D. YOUNG & CO.
Attn. HARDING, Charles T
21 New Fetter Lane
London EC4A 1DA
UNITED KINGDOM

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference PCT 448 1 CTH	Date of mailing *(day/month/year)* 07/07/1998 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 97/03352	International filing date *(day/month/year)* 04/12/1997
Applicant IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY .... et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Maurizio Amodeo

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PCT 448 1 CTH		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 97/ 03352	04/12/1997	05/12/1996
Applicant		
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY .... et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [X] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/03352

Box I Observations where certain claims were found unsearchabl (Continuati n of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 32
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See further information sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims : 1-19, 28-31(partly) Ortho-substituted aryl sulphamate compounds of formula (I), pharmaceutical compositions and uses thereof.
2. Claims : 20-30, 28-31(partly) 17-Unsubstituted estrogen-3-sulpha mates of formula (X), pharamceutical compositions and uses thereof.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 32

Claim 32 defines its subject matter by reference to the description and figures, in clear violation of Rule 6.2(a) PCT. In addition this claim qualifies the subject matter to be drawn from the description thus "A sulphamate compound SUBSTANTIALLY as herein described and with reference to any one of figures 2 to 11". The use of the wording "substantially" indicates that not all of the subject matter of the description and figures 2 to 11 is to be contstrued as being included in this claim, but does not clarify which subject matter is to be included in claim 32 and which is to be excluded. Consequently, the true scope and subject matter of this claim is rendered so unclear according to Article 6 PCT, that no search could be carried out thereon.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/03352

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J41/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	DE 44 29 398 A (JENAPHARM GMBH) 15 February 1996 see page 4, line 36 - line 37 see page 5, line 55 - line 64 see page 6, line 6 ---	1-19, 28-31 1-31
X	L. WOO ET AL: "Active Site Directed Inhibition of Estrone Sulfatase by Nonsteroidal Coumarin Sulfamates" JOURNAL OF MEDICINAL CHEMISTRY., vol. 39, no. 7, 29 March 1996, WASHINGTON US, pages 1349-1351, XP002059345 see page 1350, column 1; figure 3 see page 1349, column 2 see page 1350, column 2; figure 5 --- -/--	1-5, 10-16, 19,28-31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 1998	07. 07. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, P

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. FISHMAN ET AL: "Studies on the Directive O-Methylation of Catechol Estrogens" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 89, no. 26, 1967, DC US, pages 7147-7148, XP002059346 see page 7148, column 1, paragraph 1 ---	1-19, 28-31
Y	WO 93 05064 A (IMPERIAL COLLEGE) 18 March 1993 see examples 1-8 ---	1-31
Y	R. PETERS ET AL: "Analogues of [(Triethylsily)ethynyl]estradiol as Potential Antifertility Agents" JOURNAL OF MEDICINAL CHEMISTRY., vol. 31, no. 3, 1988, WASHINGTON US, pages 572-576, XP002059347 see page 572, column 2, paragraph 2 see in particular compounds 1,2,4 and 8 see page 574; table II ---	1-19, 28-31
Y	R. RAJAN ET AL: "Estrogen Effects on NADH Oxidase and Superoxide Dismutase in Prepubertal Female Rats" STEROIDS., vol. 40, no. 6, 1982, SAN FRANCISCO US, pages 651-660, XP002059348 see page 654, column 2; table 1 ---	1-19, 28-31
Y	M. CUSHMAN ET AL: "Synthesis, Antitubulin and Antimitotic Activity, and Cytotoxicity of Analogs of 2-Methoxyestradiol, an Endogenous Mammalian Metabolite of Estradiol That Inhibits Tubulin Polymerization by Binding to the Colchicine Binding Site" JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 12, 9 June 1995, WASHINGTON US, pages 2041-2049, XP002059349 see page 2043; table 1 see in particular compounds 1, 8a, 10b, 15 and 23 see page 2045, column 1; table 3 ---	1-19, 28-31
Y	C. LOVELY ET AL: "2-(Hydroxyalkyl)estradiols: Synthesis and Biological Evaluation" JOURNAL OF MEDICINAL CHEMISTRY., vol. 39, no. 9, 26 April 1996, WASHINGTON US, pages 1917-1923, XP002059350 see page 1919; table 2 ---	1-19, 28-31

-/--

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 107, no. 21, 23 November 1987 Columbus, Ohio, US; abstract no. 190359, S. BROOKS ET AL: "A-Ring substituted estrogens as inhibitors of the MXT transplantable mammary ductal carcinoma" page 18; column 2; XP002059352 see abstract & CANCER RESEARCH, vol. 47, no. 17, 1987, pages 4623-4629, ---	1-19, 28-31
Y	US 4 668 668 A (BROOKS SAMUEL C ET AL) 26 May 1987 see the whole document ---	1-19, 28-31
Y	TOWNSLEY J D: "Further studies on the regulation of human placental steroid 3-sulfatase activity" ENDOCRINOLOGY, vol. 93, no. 1, 1973, pages 172-181, XP002068155 see page 178, table 6, entry 16 ---	20-31
Y	CHEMICAL ABSTRACTS, vol. 068, no. 1, 1 January 1968 Columbus, Ohio, US; abstract no. 009640, ADAMS J B: "Enzymic synthesis of steroid sulfates. V. Binding of estrogens to estrogen sulfotransferase" page 913; column 2; XP002068156 see abstract & BIOCHIMICA ET BIOPHYSICA ACTA , vol. 146, no. 2, 1967, pages 522-528, ---	20-31
P,X	S. SCHWARZ ET AL: "Synthesis of estrogen sulfamates: Compounds with a novel endocrinological profile" STEROIDS., vol. 61, no. 12, December 1996, SAN FRANCISCO US, pages 710-717, XP002059351 see page 713, compound 9 see page 710, column 1, paragraph 1 -----	1-7, 10-12,19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/03352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4429398 A	15-02-1996	AU 2974295 A	07-03-1996
		BR 9508868 A	28-10-1997
		CA 2196678 A	22-02-1996
		CZ 9700273 A	13-08-1997
		DE 4447714 C	05-02-1998
		DE 4447715 C	05-02-1998
		WO 9605217 A	22-02-1996
		EP 0775156 A	28-05-1997
		NO 970569 A	08-04-1997
		PL 318530 A	23-06-1997
		SG 33434 A	18-10-1996
		SK 16297 A	06-08-1997
WO 9305064 A	18-03-1993	AU 668882 B	23-05-1996
		AU 2490592 A	05-04-1993
		AU 689043 B	19-03-1998
		AU 5837396 A	05-09-1996
		BR 9206434 A	27-09-1994
		CA 2114630 A	18-03-1993
		CZ 9400440 A	18-01-1995
		EP 0641355 A	08-03-1995
		FI 940903 A	20-04-1994
		HU 66097 A	28-09-1994
		JP 7501515 T	16-02-1995
		NO 940635 A	29-04-1994
		SK 24694 A	09-11-1994
		US 5616574 A	01-04-1997
US 4668668 A	26-05-1987	US 4568673 A	04-02-1986
		US 4636496 A	13-01-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/03352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4429398 A	15-02-1996	AU 2974295 A	07-03-1996
		BR 9508868 A	28-10-1997
		CA 2196678 A	22-02-1996
		CZ 9700273 A	13-08-1997
		DE 4447714 C	05-02-1998
		DE 4447715 C	05-02-1998
		WO 9605217 A	22-02-1996
		EP 0775156 A	28-05-1997
		NO 970569 A	08-04-1997
		PL 318530 A	23-06-1997
		SG 33434 A	18-10-1996
		SK 16297 A	06-08-1997
WO 9305064 A	18-03-1993	AU 668882 B	23-05-1996
		AU 2490592 A	05-04-1993
		AU 689043 B	19-03-1998
		AU 5837396 A	05-09-1996
		BR 9206434 A	27-09-1994
		CA 2114630 A	18-03-1993
		CZ 9400440 A	18-01-1995
		EP 0641355 A	08-03-1995
		FI 940903 A	20-04-1994
		HU 66097 A	28-09-1994
		JP 7501515 T	16-02-1995
		NO 940635 A	29-04-1994
		SK 24694 A	09-11-1994
		US 5616574 A	01-04-1997
US 4668668 A	26-05-1987	US 4568673 A	04-02-1986
		US 4636496 A	13-01-1987

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PCT 448 1 CTH

Box No. I TITLE OF INVENTION

COMPOUND

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Imperial College of Science Technology and Medicine
Sherfield Building
Exhibition Road
London
SW7 2AZ

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

REED, Michael John
Unit of Metabolic Medicine
Imperial College School of Medicine, St Mary's Hospital
Norfolk Place
Paddington
London
W2 1PG

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

HARDING, Charles Thomas
D Young & Co
21 New Fetter Lane
London
EC4A 1DA
United Kingdom

Telephone No. +44 1703 634816

Facsimile No. +44 1703 224262

Teleprinter No. 477667 YOUNGS G

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

POTTER, Barry Victor Lloyd
Department of Pharmacy and Pharmacology
Faculty Of Science
University of Bath
Claverton Down
Bath
BA2 7AY

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ HU Hungary
- ☒ IL Israel
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America
- ☒ UZ Uzbekistan
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZW Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ Indonesia
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

See Notes to the request form

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:	*in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;*
in particular:	
(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:	*in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below;*
(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents:	*in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":	*in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
(vi) if there are more than three earlier applications whose priority is claimed:	*in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:	***in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.***

PURVIS, William Michael Cameron
COTTER, Ivan John
PILCH, Adam John Michael
CRISP, David Norman
ROBINSON, Nigel Alexander Julian
HARRIS, Ian Richard
TURNER, James Arthur
MALLALIEU, Catherine Louise
PRICE, Paul Anthony King
PRATT, Richard Wilson
HOLMES, Miles Keeton
HORNER, David
MASCHIO, Antonio
NACHSHEN, Neil

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) United Kingdom	5 Dec 96	9625334.9	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 5	sheets
2. description	: 25	sheets
3. claims	: 5	sheets
4. abstract	: 1	sheets
5. drawings	: 7	sheets
Total	: 43	sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other *(specify)*:

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

ANTONIO MASCHIO

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: PCT 448 1 CTH

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB97/03352	4 Dec 1997	5 Dec 1996

Title of invention: COMPOUND

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Imperial College of Science, Technology and Medicine
Sherfield Building
Exhibition Road
London
SW7 2AZ

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

REED, Michael John
Unit of Metabolic Medicine
Imperial College School of Medicine, St Mary's Hospital
Norfolk Place
Paddington
London
W2 1PG

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

POTTER, Barry Victor Lloyd
Department of Pharmacy and Pharmacology
Faculty of Science
University of Bath
Claverton Down
Bath
BA2 7AY

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/GB97/03352

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☑ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HARDING, Charles Thomas
D Young & Co
21 New Fetter Lane
London
EC4A 1DA
United Kingdom

Telephone No.: +44 1703 634816

Facsimile No.: +44 1703 224262

Teleprinter No.: 477667 YOUNGS G

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

(i) ☑ to start the international preliminary examination on the basis of the international application as originally filed.

(ii) ☐ to take into account the amendments under Article 34 of

☐ the description (amendments attached).

☐ the claims (amendments attached).

☐ the drawings (amendments attached).

(iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

☑ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except:

(if the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

National application No.
PCT/GB97/03352

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. amendments under Article 34				
description	:	sheets	☐	☐
claims	:	sheets	☐	☐
drawings	:	sheets	☐	☐
2. letter accompanying amendments under Article 34	:	sheets	☐	☐
3. copy of amendments under Article 19	:	sheets	☐	☐
4. copy of statement under Article 19	:	sheets	☐	☐
5. other *(specify)*	:	sheets	☐	☐

The demand is also accompanies by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☑ fee calculation sheet
5. ☑ other *(specify)*:

Letter

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

C T HARDING

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the xpiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07J 41/00 — A2

(11) International Publication Number: WO 98/24802

(43) International Publication Date: 11 June 1998 (11.06.98)

(21) International Application Number: PCT/GB97/03352

(22) International Filing Date: 4 December 1997 (04.12.97)

(30) Priority Data:
9625334.9 5 December 1996 (05.12.96) GB

(71) Applicant *(for all designated States except US)*: IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE [GB/GB]; Sherfield Building, Exhibition Road, London SW7 2AZ (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: REED, Michael, John [GB/GB]; Imperial College School of Medicine, St. Mary's Hospital, Unit of Metabolic Medicine, Norfolk Place, Paddington, London W2 1PG (GB). POTTER, Barry, Victor, Lloyd [GB/GB]; University of Bath, Faculty of Science, Dept. of Pharmacy and Pharmacology, Claverton Down, Bath BA2 7AY (GB).

(74) Agents: HARDING, Charles, Thomas et al.; D Young & Co., 21 New Fetter Lane, London EC4A 1DA (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOUND

(57) Abstract

A compound is described. The compound is suitable for use as an inhibitor of oestrone sulphatase. The compound has formula (I); wherein A is a first group; B is an aryl ring structure having at least 4 carbon atoms in the ring and wherein the ring B is substituted in at least the 2 position and/or the 4 position with an atom or group other than H; X is a sulphamate group; wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and wherein group A is attached to at least one carbon atom in ring B.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HARDING, Charles T.
D. YOUNG & CO.
21 New Fetter Lane
London EC4A 1DA
GRANDE BRETAGNE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	08.12.98
Applicant's or agent's file reference: PCT 448 1 CTH	**REPLY DUE** within ~~3 month(s)~~ 2 months from the above date of mailing

International application no.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB97/03352	04/12/1997	05/12/1996

International Patent Classification (IPC) or both national classification and IPC
C07J41/00

Applicant
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY .... et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and / or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 05/04/1999

Name and mailing address of the international preliminary examining authority
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer / Examiner
Friebel, F

Formalities officer (incl. extension of time limits)
Gallego, A
Telephone No. (+49-89) 2399-8102

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-25 as originally filed

Claims, No.:

1-36 as received on 22/07/1998 with letter of 20/07/1998

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 19 and 32,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 19 and 32 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6, 10-16, 28-31, 33-35 - NO
Inventive step (IS)	Claims	7-9, 17, 18, 20-27, 36 - NO
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

point III:

Claims 19 and 32 are so unclear that no meaningful examination is possible. Claim 19 has been already briefly adressed in the Form 405 invitation and as concerns Claim 32 the Applicant is directed to the criticism expressed by the Search Examiner in the Intern.Search Report of 7.7.98.

point V:

The application contains two distinct inventions which will be dealt with separately starting with the

1st invention: ortho-substituted aryl sulphamate compounds of formula (I), pharmaceutical compositions and use thereof

Closest prior art are the documents **DE-A-4429398 (D1)** and **L.W.L.WOO et al. J.Med.Chem. 39, 1349 (1996) (D2)** (Art.33(2) PCT). From D1 ortho-substituted estra-1,2,5(10)-triene-3-sulphamate derivatives are already known; see in particular the two compounds mentioned in line 36 and line 37 of page 4, whereas D2 refers to the second class of compounds: the non-steroidal derivatives. In particular relevant is here the compound 15 of Fig.3 on page 1350. It should be noted that D2 explicitely refers to the development of estrone sulfatase inhibitiors.

As concerns the feature of ortho-substitution, the paper of **M.CUSHMAN et al. J.Med.Chem. 38, 2041 (1995) (D3)** as well as of **C.J.LOVELY et al. J.Med. Chem. 39, 1917 (1996) (D4)** are deemed to be relevant. From these documents it is known that a substituent at C-2 of the steroidal skeleton lowers the affinity to the estrogen receptor. The Applicant's attention is directed to the left col. on page 2045 of D3 (Tab.3 and the last full paragraph) and to D4, the left col. on page 1919; under 'Biological Evaluation' it is stressed that "*The estradiol homologs exhibited significantly weaker affinity for the estrogen receptor than estradiol, ...*"

Sulphatase inhibition in combination with no, or a minimal oestrogenic effect is the problem underlying the instant application; see the paragraph bridging pages 2 and 3 of the description. The solution to this problem seems to be the substitution of the A-ring (or A-ring equivalent) in ortho position to the amidosulfonate function. This however, is deemed to be obvious in the light of the teaching of the documents D3 and D4 (Art.33(3) PCT).

As concerns the document S.SCHWARZ et al. Steroids 61, 710 (1996) the IPEA assumes that the present application is entitled to the priority date claimed.

2nd invention: C-17 unsubstituted estrogen-3-sulphamates of formula X, pharmaceutical compositions and use thereof

C-17 unsubstituted estrogens with a C-3 sulphamate group are not disclosd in the available prior art; novelty is therefore acknowledged (Art.33(2) PCT).

As concerns inventive step, the two papers of **TOWNSLEY** and **ADAMS** cited in the Intern.Search Report are deemed to be relevant: **Endocrinology 93/1, 172 (1972) (D5)** and **Biochem.Biophys.Acta 146, 522 (1967) (D6)**. D5 discloses various steroidal sulfatase inhibitors, inter alia the C-17 unsubstituted derivative 1,3,5(10)estratriene-3,16 -α-diol (compound 16 of Table 6). Furthermore, from D6 it is known that 17-deoxyestrone binds to estrogen sulphotransferase. The modification of the C-OH function by esterification with sulfamic acid is well known in the field of estrone sulphatase inhibitors (see the first part of this communication). To further remove the oxygen from C-17 and to leave this position unmodified is made obvious by the reference D5. The subject-matter of the 2nd invention seems therefore to be deprived of an inventive step (Art.33(3) PCT).

point VII:

To meet the requirement of Rule 5.1(a)(ii) PCT the references D1, D2 and D5 should be briefly summarized in the description.

point VIII:

Various claims do not meet the clarity requirement of Art.6 PCT; see the invitation to restrict or to pay additional fees of 2.10.98.

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In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HARDING, Charles T.
D. YOUNG & CO.
21 New Fetter Lane
London EC4A 1DA
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 11.03.99
Applicant's or agent's file reference PCT 448 1 CTH	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB97/03352	04/12/1997	05/12/1996

Applicant
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY .... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	DA ROCHA, O. Tel.(+49-89) 2399-8101

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT 448 1 CTH		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB97/03352	04/12/1997	05/12/1996
International Patent Classification (IPC) or national classification and IPC		
C07J41/00		
Applicant		
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY .... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/07/1998	11.03.99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Friebel, F Telephone No. (+49-89) 2399 8552

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/03352

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-25 as originally filed

Claims, No.:

1-36 as received on 22/07/1998 with letter of 20/07/1998

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 19 and 32.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 19 and 32 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. R asoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-9, 17, 18, 20-27, 28-31 (2nd inv.), 36
	No:	Claims	1-6, 10-16, 28-31 (1st inv.), 33-35
Inventive step (IS)	Yes:	Claims	
	No:	Claims	7-9, 17, 18, 20-27, 28-31, 36
Industrial applicability (IA)	Yes:	Claims	1-18, 20-31, 33-36
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

point III:

Claims 19 and 32 are so unclear that no meaningful examination is possible.

point IV:

The present application claims for two distinct inventions:
- ortho-substituted aryl sulphamate compounds of formula (I), pharmaceutical compositions and use thereof,
- C-17 unsubstituted estrogen-3-sulphamates of formula (X), pharmaceutical compositions and use thereof;

A complete Search Report was issued on 7.7.98.

The IPEA concurs with the non-unity objection of the Search Examiner; see in particular the paper of L.W.L.WOO et al. in J.Med.Chem., the Search Examiner already referred to.

point V:

The application contains two distinct inventions which will be dealt with separately starting with the
1st invention: ortho-substituted aryl sulphamate compounds of formula (I), pharmaceutical compositions and use thereof **(Claims 1-18, 28-31, 33-36)**

Closest prior art are the documents **DE-A-4429398 (D1)** and **L.W.L.WOO et al. J.Med.Chem. 39**, 1349 (1996) (D2) (Art.33(2) PCT). From D1 ortho-substituted estra-1,2,5(10)-triene-3-sulphamate derivatives are already known; see in particular the two compounds mentioned in line 36 and line 37 of page 4, whereas D2 refers to the second class of compounds: the non-steroidal derivatives. In particular relevant is here the compound 15 of Fig.3 on page 1350. It should be noted that D2 explicitely refers to the development of estrone sulfatase inhibitiors.

As concerns the feature of ortho-substitution, the paper of **M.CUSHMAN et al. J.Med.Chem. 38**, 2041 (1995) (D3) as well as of **C.J.LOVELY et al. J.Med. Chem. 39**, 1917 (1996) (D4) are deemed to be relevant. From these documents it is known that a substituent at C-2 of the steroidal skeleton lowers the affinity to the estrogen receptor. The Applicant's attention is directed to the left col. on page

2045 of D3 (Tab.3 and the last full paragraph) and to D4, the left col. on page 1919; under 'Biological Evaluation' it is stressed that "The estradiol homologs exhibited significantly weaker affinity for the estrogen receptor than estradiol, ..."

The subject-matter of Claims 1-6, 10-16, 28-31 and 33-35 does not meet the novelty requirement of Art. 33(2) PCT.

Sulphatase inhibition in combination with no, or a minimal oestrogenic effect is the problem underlying the instant application; see the paragraph bridging pages 2 and 3 of the description. The solution to this problem seems to be the substitution of the A-ring (or A-ring equivalent) in ortho position to the amidosulfonate function. This however, is deemed to be obvious in the light of the teaching of the documents D3 and D4; therefore Claims 7-9, 17, 18 and 36 are deemed to be obvious (Art.33(3) PCT).

As concerns the document S.SCHWARZ et al. Steroids 61, 710 (1996) the IPEA assumes that the present application is entitled to the priority date claimed.

2nd invention: C-17 unsubstituted estrogen-3-sulphamates of formula X, pharmaceutical compositions and use thereof **(Claims 20-31)**

C-17 unsubstituted estrogens with a C-3 sulphamate group are not disclosd in the available prior art; novelty is therefore acknowledged for Claims 20-31 (Art.33(2) PCT); Claims 28 to 31 in that they refer to the 2nd invention.

As concerns inventive step, the two papers of **TOWNSLEY** and **ADAMS** cited in the Intern.Search Report are deemed to be relevant: **Endocrinology 93/1**, 172 **(1972) (D5)** and **Biochem.Biophys.Acta 146**, 522 (1967) (D6). D5 discloses various steroidal sulfatase inhibitors, inter alia the C-17 unsubstituted derivative 1,3,5(10)estratriene-3,16 -α-diol (compound 16 of Table 6). Furthermore, from D6 it is known that 17-deoxyestrone binds to estrogen sulphotransferase. The modification of the C-OH function by esterification with sulfamic acid is well known in the field of estrone sulphatase inhibitors (see the first part of this communication). To further remove the oxygen from C-17 and to leave this position

CLAIMS

1. A sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, wherein the compound has the Formula I; wherein A is a first group; B is an aryl ring structure having at least 4 carbon atoms in the ring and wherein the ring B is substituted in at least the 2 position and/or the 4 position with an atom or group other than H; X is a sulphamate group; wherein group A and ring B together are capable of mimicking the A and B rings of oestrone; and wherein group A is attached to at least one carbon atom in ring B.

2. A sulphamate compound according to claim 1 wherein the sulphamate group is at position 3 of the ring B.

3. A sulphamate compound according to claim 1 or claim 2 wherein the ring B has six carbon atoms in the ring.

4. A sulphamate compound according to any one of the preceding claims wherein the compound has the Formula II; wherein X is the sulphamate group of any one of claims 1 to 3; A is the first group according of any one of claims 1 to 3; R_1 and/or R_2 is a substituent other than H; wherein R_1 and R_2 may be the same or different but not both being H; and wherein optionally group A is attached to at least one other carbon atom in ring B.

5. A sulphamate compound according to claim 4 wherein group A is additionally attached to the carbon atom at position 1 of the ring B.

6. A sulphamate compound according to any one of the preceding claims wherein the compound has the Formula IV; wherein X is the sulphamate group of any one of claims 1 to 5; R_1 and/or R_2 is a substituent other than H; wherein R_1 and R_2 may be the same or different but not both being H; and wherein Y is a suitable linking group.

7. A sulphamate compound according to claim 6 wherein Y is $-CH_2-$ or -C(O)-.

8. A sulphamate compound according to claim 7 wherein Y is -C(O)-.

9. A sulphamate compound according to any one of the preceding claims wherein the compound has the Formula V; wherein X is the sulphamate group of any one of claims 1 to 8; R_1 and/or R_2 is a substituent other than H; and wherein R_1 and R_2 may be the same or different but not both being H.

10. A sulphamate compound according to any one of the preceding claims wherein the sulphamate group has the Formula III; wherein each of R_3 and R_4 is independently selected from H, alkyl, cycloalkyl, alkenyl and aryl, or together represent alkylene optionally containing one or more hetero atoms or groups in the alkylene chain.

11. A sulphamate compound according to claim 10 wherein at least one of R_3 and R_4 is H.

12. A sulphamate compound according to claim 11 wherein each of R_3 and R_4 is H.

13. A sulphamate compound according to any one of claims 4 to 12 wherein each of R_1 and R_2 is independently selected from H, alkyl, cycloalkyl, alkenyl, aryl, substituted alkyl, substituted cycloalkyl, substituted alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy containing group.

14. A sulphamate compound according to claim 13 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} cycloalkyl, C_{1-6} alkenyl, substituted C_{1-6} alkyl, substituted C_{1-6} cycloalkyl, substituted C_{1-6} alkenyl, substituted aryl, a nitrogen containing group, a S containing group, or a carboxy group having from 1-6 carbon atoms.

15. A sulphamate compound according to claim 14 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, a nitrogen containing group, or a carboxy group having from 1-6 carbon atoms.

16. A sulphamate compound according to claim 15 wherein each of R_1 and R_2 is independently selected from H, C_{1-6} alkyl, C_{1-6} alkenyl, NO_2, or a carboxy group having from 1-6 carbon atoms.

17. A sulphamate compound according to claim 16 wherein each of R_1 and R_2 is independently selected from H, C_3 alkyl, C_3 alkenyl, NO_2, or H_3CHO.

18. A sulphamate compound according to claim 17 wherein the compound is any one of the Formulae VI - IX.

19. A sulphamate compound according to any one of the preceding claims wherein the compound is further characterised by the feature that if the sulphamate group were to be substituted with a sulphate group to form a sulphate derivative, then the sulphate derivative would be hydrolysable by an enzyme having steroid sulphatase (E.C. 3.1.6.2) activity.

AMENDED SHEET

27. A sulphamate compound according to claim 26 wherein each of R_3 and R_4 is H.

28. A sulphamate compound according to any one of the preceding claims for use as a pharmaceutical.

29. A sulphamate compound according to any one of claims 1 to 27 for inhibiting oestrone sulphatase.

30. A pharmaceutical composition comprising a sulphamate compound according to any one of claims 1 to 27; and a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

31. Use of a sulphamate compound according to any one of claims 1 to 27 in the manufacture of a pharmaceutical for inhibiting oestrone sulphatase.

32. A sulphamate compound substantially as described herein and with reference to any one of Figures 2 to 11.

33. A sulphamate compound according to claim 1 wherein the group A/ring B combination contains one or more alkoxy substituents.

34. A sulphamate compound according to claim 1 wherein the group A/ring B combination contains one or more methoxy substituents.

35. A sulphamate compound according to claim 13 wherein R_1 and/or R_2 is an alkoxy group.

36. A sulphamate compound according to claim 35 wherein R_2 is an alkoxy group.